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EXAMINER

KIM, YOUNG J

ART UNIT

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1637

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ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

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Advisory Action

The present Office Action is responsive to the Amendment received on July 16, 2010.

Claim Rejections - 35 USC § 112

The rejection of claims 1-11, 13, 14, 19-21, 24-30, and 32 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter, made in the Office Action mailed on May 18, 2010 is withdrawn in view of the Amendment received on July 16, 2010.

Claim Rejections - 35 USC § 102

The rejection of claims 1-3, 5, and 7-10 under 35 U.S.C. 102(a) and (e) as being anticipated by Mukai et al. (US 2003/0073081 A1, published April 17, 2003, filed August 23, 2001), made in the Office Action mailed on May 18, 2010 is withdrawn in view of the arguments presented in the Amendment received on July 16, 2010.

Rejection, Maintained

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The rejection of claims 1-3, 7-11, 24, 25, and 27-30 under 35 U.S.C. 102(b) as being anticipated by Bohlander, S.K. (U.S. Patent No. 5,731,171, issued March 24, 1998), made in the Office Action mailed on May 18, 2010 is maintained for the reasons already of record.

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Applicants' arguments presented in the Amendment received on July 16, 2010 have been fully considered but they are not found persuasive for the reasons set forth in the, "Response to Arguments" section.

The Rejection:

Bohlander discloses a reagent composition comprising:

each of dATP, dCTP, dGTP, and dTTP ("following conditions: ... 150 uM each dATP, dGTP, and dCTP, 110 uM dTTP...") in combination with dUTP ("... 40 uM Bio-11-dUTP..."), wherein said dUTP is at about 10 to 50% of dTTP ($40/110 = 37\%$ of dTTP is dUTP), wherein said mixture comprises a fluorescent probe, beacon or intercalating dye ("products may also be labeled with the fluorophore Spectrum-Orange" column 20, lines 59-63), thereby anticipating claim 1.

Bohlander detects the amplified product (see column 24, lines 33-36, hybridization against cDNA libraries on solid support).

With regard to claims 2 and 3, the artisans also contemplate a mixture comprising 150 uM of each dNTPs and 30 uM of dUTP, which translates to the presence of dUTP at 20% of dTTP concentration.

With regard to claims 7 and 8, the concentration of dUTP (40 uM or 30 uM) does not exceed 300 or 100 uM.

With regard to claims 9 and 10, the artisans disclose that the composition comprises a polymerase (Taq DNA polymerase, see column 20, lines 50-54), and a buffer system (Tris HCl).

Therefore, Bohlander anticipates the invention as claimed.

Response to Arguments:

Applicants traverse the rejection.

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Applicants state that the Office erroneously (1) assumes that the plain and customary definition of dUTP encompasses functionalized/conjugated dUTP, (2) disregards the definition of dUTP as set forth by the Applicant, (3) interprets dUTP more broadly than is reasonable in light of the specification, and (4) ignores a wherein clause indicating that the inclusion of dUTP reduces the formation of primer aggregates during the amplification reaction in comparison with an amplification reaction employing only conventional nucleotides (page 5 bottom to page 6, 1st paragraph).

1 – The Office erroneously assumes the plain and customary definition of dUTP:

Applicants state that “[f]or the record, ... the Office has mistakenly construed the ordinary and customary meaning of dUTP to encompass a functionalized/conjugated dUTP. Applicants contend that the term, “dUTP” is merely a well-known abbreviation for the nucleic acid deoxyuridine triphosphate and, absent any teaching to the contrary, cannot automatically be interpreted to include functionalized/conjugated dUTP absent adequate basis in the specification.

Applicants state that if the ordinary and customary meaning of dUTP were to encompass a functionalized/conjugated dUTP, the ordinary skilled artisan would not have to distinguish between unfunctionalized/unconjugated dUTP and functionalized/conjugated dUTP. Applicants contend that furthermore, a patent drafter would not have to change the definition of dUTP to include functionalized/conjugated dUTP (page 6, 2nd paragraph, Response).

This argument has been well considered but has not been found persuasive because based on a reasonable broadest interpretation, dUTP does embrace conjugated forms and functionalized forms.

The rationale was clearly relayed to Applicants. The rationale is reiterated herein and it is maintained herein that a generic recitation of dUTP embraces all forms of dUTP.

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Consider for example, an independent claim 1 drawn to a composition comprising dUTP. consider a dependent claim which depend from said independent claim which recites, “the composition of claim 1, wherein said dUTP is a Bio-11-dUTP.” Would this dependent claim be a proper dependent claim? Obviously, the answer to that question would be a “yes,” since the generic recitation of the term, “dUTP” embraces all subspecies therein, including but not limited to conjugated dUTPs such as Bio-11-dUTP.

Analogously, consider a claim limitation drawn to a mixture comprising dUTP. Then consider a **further limiting** claim that depends from that claim, reciting that the dUTP comprises a biotinylation. Based on Applicants' claim construction, such dependent claim would not a proper dependent claim because generic recitation of dUTP precludes any of its modified form such as labeling, conjugation, etc.

Clearly, Applicants' reasoning is erroneous. In fact, if Applicants are insistent that their claim does not embrace functionalized/conjugated forms of dUTPs, then Applicants are invited to recite the limitation into the claims.

2 – The Office disregard the definition of dUTP set forth by Applicants:

Applicants state that “[r]egardless of whether the Office agrees that the ordinary and customary meaning of dUTP excludes functionalized/conjugated dUTP, an interpretation otherwise erroneously disregards the definition of dUTP as set forth by the Applicant (page 7, 2nd paragraph, Response).

Applicants state that, “[h]ere, Applicants have consistently asserted that dUTP refers only to deoxyuridine triphosphate and that the specification consistently uses dUTP to refer only to deoxyuridine triphosphate (page 7, 2nd paragraph, Response).

If Applicants are inferring prosecution estoppel based on their arguments that dUTP does not embrace its conjugated/functionalized counterparts, such statement has no bearing if the specification does not clearly support Applicants' position:

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“It is applicant’s burden to precisely define the invention, and not the [examiner’s].” *In re Morris*, 127 F.3d 1048, 1056, 44 USPQ2d 1023, 1029 (Fed. Cir. 1997).

Therefore, it would not be proper for the Office to give words of the claim special meaning when no such special meaning has been defined by Applicants in the written description.

3 - The Office interprets dUTP more broadly than is reasonable in light of the specification:

As to the specification’s definition of the term, “dUTP,” there is no explicit definition which limits dUTP to its non-conjugated/non-functionalized counterparts. In fact, there isn't an explicit definition found anywhere in the specification for the claim term.

As to Applicants arguments drawn to the mixture being used in a reaction involving UNG (page 8, 1st paragraph, Response), a product is defined by its physical attributes and not based on its intended usage.

4 - The Office ignores the limitation set forth by the wherein clause:

Lastly, Applicants contend that the specification teaches that unlike the prior art, the present invention uses dUTP to reduce formation of primer aggregates and that a skilled artisan reading the specification would not interpret dUTP to include functionalized/conjugated dUTP since a functionalized/conjugated dUTP is unlikely to reduce the formation of primer aggregates (page 8, 2nd paragraph, Response).

As to whether or not the generic recitation of dUTP includes its conjugated/functionalized counterpart, this issue was already discussed above.

As to Applicants’ assertion in the ability of the mixture disclosed by Bolander et al. to reduce primer aggregation, such assertion is not accompanied by evidence. It appears to be Applicants' assumption.

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According to *In re Best* 195 USPQ 430, 1997, the court stated that, “Patent Office can require *applicant to prove that prior art products do not necessarily or inherently possess characteristics of his claimed product wherein claimed and prior art products are identical or substantially identical*, or are produced by identical or substantially identical processes; burden of proof is on applicant” (pp. 430).

Applicants are invited to present factual evidence of side-by-side comparison of the mixture of Bolander et al. and the mixture of instant application. Absent evidence to the contrary, assertion without factual evidence would not be deemed convincing.

For the above reasons, the rejection is maintained for the reasons of record.

Claim Rejections - 35 USC § 103

The rejection of claims 4 and 6 under 35 U.S.C. 103(a) as being unpatentable over Mukai et al. (US 2003/0073081 A1, published April 17, 2003, filed August 23, 2001) in view of McLaughlin et al. (U.S. Patent No. 6,783,940 B2, issued August 31, 2004, filed October 31, 2001; cited previously), made in the Office Action mailed on May 18, 2010 is withdrawn in view of the arguments presented in the Amendment received on July 16, 2010.

Rejection, Maintained

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

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The rejection of claims 13, 14, 19, 20, 21, 26, and 32 under 35 U.S.C. 103(a) as being unpatentable over Bohlander, S.K. (U.S. Patent No. 5,731,171, issued March 24, 1998) in view of McLaughlin et al. (U.S. Patent No. 6,783,940 B2, issued August 31, 2004, filed October 31, 2001; cited previously), made in the Office Action mailed on May 18, 2010 is maintained for the reasons already of record.

In the Amendment received on July 16, 2010, Applicants' do not present any new arguments for the present rejection and therefore, the rejection is maintained herein.

The Rejection:

The teachings of Bohlander et al. have already been discussed above.

Bohlander et al. do not teach the use of mannitol or sorbitol.

McLaughlin et al. disclose that sorbitol reduces non-specific amplification in a DNA polymerase chain reaction involving sorbitol (column 2, lines 13-15), with said sorbitol concentration ranging from 0..25M to 0.35M (which is 250 mM to 350 mM, respectively; column 2, lines 25-27).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Bohlander et al. with the teachings of McLaughlin et al., thereby arriving at the claimed invention for the following reasons.

As Bohlander et al. demonstrate a method of amplifying a target nucleic acid sequence using PCR primers, said one of ordinary skill in the art would have been reasonably motivated to employ other reagent means which would also further aid in specific target amplification, such as that of McLaughlin et al.

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In *KSR International Co. v. Teleflex Inc. (KSR)*, (citation omitted), the Supreme Court expressed that, “[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.” *Id.* at ___, 82 USPQ2d at 1395.

Clearly, one of ordinary skill in the art at the time the invention was made would have recognized that adding art-recognized amounts of sorbitol in an amplification reaction mixture, as evidenced by McLaughlin et al., would have resulted in the predictable result of providing higher specificity in amplification reaction.

Additionally, the MPEP, at 2143.02, states that the prior art can be modified or combined to reject claims as obvious as long as there is a reasonable expectation of success.

To this end, McLaughlin et al. state the following:

“Other dNTPs, such as deoxyuridine triphosphate (“dUTP”), and dNTP analogs [**which would be considered to be non-conventional nucleotides**], and conjugated dNTPs may also be used...” (column 6, lines 19-22; McLaughlin et al.)

“Deoxynucleotide triphosphates (“dNTPs”), which are the building blocks of the amplification nucleic acid molecules, are typically supplied in standard PCR reactions at a concentration of 40-200 M each ...” (column 6, lines 14-17) with contemplation of, “higher than 200 M...” being advantageous (column 6, lines 25-26; McLaughlin et al.)

Provided that McLaughlin et al. explicitly state that the reagents employed by Bohlander et al. (dNTPs including dUTPs in PCR reactions) are combinable and workable at the same ranges (40-200 M each, and higher than 200 M), one of ordinary skill in the art would have had no doubt that the combination of the teaching would have been successful.

As to the primers, wherein all the thymidines are completely replaced by uracil, such modification would have been obvious to one of ordinary skill in the art, for the purpose of generating amplicons which comprises all uracil bases in the amplified products.

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Lastly, with respect to the new claim 32, Bohlander et al. explicitly disclose that their amplification reaction involve a melting temperature of more than about 60°C (column 3, lines 50-51; column 4, lines 5-8).

Therefore, for the above reasons, the invention as claimed is *prima facie* obvious over the cited references.

Conclusion

No claims are allowed.

Inquiries

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Young J. Kim whose telephone number is (571) 272-0785. The Examiner is on flex-time schedule and can best be reached from 6:00 a.m. to 2:30 p.m (M-F). The Examiner can also be reached via e-mail to Young.Kim@uspto.gov. However, the office cannot guarantee security through the e-mail system nor should official papers be transmitted through this route.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Gary Benzion, can be reached at (571) 272-0782.

Papers related to this application may be submitted to Art Unit 1637 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant does submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office. All official documents must be sent to the Official Tech Center Fax number: (571) 273-8300. For Unofficial documents, faxes can be sent directly to the Examiner at (571) 273-0785. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished

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/Young J. Kim/
Primary Examiner
Art Unit 1637
7/26/2010

/YJK/